THE IMPORTANCE OF S100_ MEASUREMENT IN THE ASSESSMENT FOR NEUROLOGICAL AND NEUROCOGNITIVE FUNCTIONS IN CARDIAC SURGERY

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This study was designed to evaluate the importance of S100_ protein in the assessment of clinical and subclinical injury during early post-operative period.

33 patients undergoing cardiopulmonary bypass (CPB) were included in the study. In addition to standard pre-operative preparation, neurological examination and Mini Mental State Examination (MMSE) were performed and these assessments were repeated on postoperative days 1 and 7. Blood samples were obtained at the start of the operation, at the end of cardiopulmonary bypass, and at postoperative 5 and 24 hours, to measure the S100_ protein levels.

No major neurological complications (stroke etc.) were observed. S100_ levels increased significantly at the end of CPB, and although these levels decreased after 5 postoperative hours, they were still higher compared to pre-CPB levels. Advanced age, and prolonged cross-clamping and CPB times were associated with higher levels of S100_ protein. Nine patients at postoperative day 1 and 3 patients at postoperative day 7 had cognitive impairment as measured by MMSE. All cases with mild cognitive impairment in MMSE at postoperative day 1 (n=9) had higher levels of S100_ protein. Also, higher S100_ levels were observed in patients with minimal impairment in MMSE on the 7th (n=3) postoperative day.

Our findings suggest that the levels of S100_ protein increase in association with predictors of cerebral injury such as advanced age and prolonged cross-clamp and CPB times, and that S100_ protein is a valuable marker that can be used for the early diagnosis of cerebral injury.

INTRODUCTION

In spite of the marked decrease in the mortality and morbidity of cardiac surgery, neurological injury remains an important cause of postoperative morbidity (1).

Clinical neurological examination, computerised tomography and magnetic resonance imaging can be used to diagnose cerebral injury. Inability to employ radiological and clinical methods of examination during surgery underscores the importance of biochemical markers for the diagnosis of cerebral injury.

Pathological and metabolic events that occur during brain ischemia caused by cardiac surgery may result in the release of metabolites into blood or cerebrospinal fluid. Neuron-specific enolase and amino acids like the cerebral isoenzyme of creatine phosphokinase are among the metabolites liberated from neurons during ischemia. S100_ is also one of these proteins.

S100 protein is a calcium binding acidic protein that is abundant in glial and Schwann cells. The brain-specific subunit, beta-beta (S100_) is found in glial and Schwann cells and usually acts as an intracellular calcium receptor protein. Furthermore, S100_ protein plays a role in axonal growth, glial proliferation, neuronal differentiation, and in the calcium balance (2).

The increase in serum levels of S100_ protein can be used for the early diagnosis of brain injury, since it is indicative of both neuronal injury and increased permeability of the blood-brain barrier (1,2). Early diagnosis allows timely interventions, minimising the neurological insult.

Our objective was to evaluate the importance of the S100_ protein in the evaluation of the clinical and subclinical neurological injury during early postoperative period.

MATERIALS AND METHODS

The study was conducted in the Department of Anesthesiology and Reanimation, GATA HEH, Istanbul, Turkey between February 2003 and May 2003. The study protocol was approved by the Ethic Committee of Marmara University Faculty of Medicine, Istanbul, Turkey. A total of 33 patients (age range: 32-73 years) undergoing cardiopulmonary bypass were included in the study. Five patients were female and all of the patients had coronary artery bypass grafting.

Routine biochemistry and complete blood counts were evaluated in all patients. Neurological and Mini Mental State Examination were performed preoperatively and on the 1st and 7th postoperative days. Patients with neurological, endocrine (diabetes) or renal (creatinine > 2 mg/dl) disorders were excluded, as were the patients requiring re-operation during postoperative period.

Patients were pre-medicated with 5 mg of diazepam (Diazem® Deva Istanbul Turkey) 35 minutes prior to the operations. Before the operation, an intravenous line was established in the antecubital area with 18-16 G catheter. Invasive arterial pressure monitoring was commenced with the cannulization of radial artery. Bispectral Index (BIS; Aspect medical models A2000 USA) was used to gauge the depth of anesthesia and to titrate the anesthetic medications. BIS is based on the linear transmission of the bispectral EEG analysis and allows for digital monitoring of the cortical electroencephalographic activity with a value between 0 and 100. The BIS value is 100 in a fully conscious patient, whereas it approaches 0 under deep anesthesia. Standard BIS probes were placed: probe number 1 on glabella; probe number 2 on forehead region; and probe number 3 anterior to tragus.

Propofol 2 mg/kg (Propofol ® Fresenius Kabi Frankfurt Germany), vecuronium 0.1 mg/kg (Norcuron® N.V.Organon Oss Netherland), and fentanyl 2 µg/kg (Fentanyl Citrate® Abbott Laboratories North Chicago USA) were administered for the induction of anesthesia. Fentanyl 1-2 µg/kg, vecuronium 0.02-0.03 mg/kg, and midazolam 0.02-0.03 mg/kg (Dormicum® Roche Basel Switzerland) mg/kg were used intermittently for the maintenance. The BIS values were kept below 55.

Following induction, Swan-Ganz catheter (Baxter Swan-Ganz catheters True models 7F USA) was placed via right internal jugular vein. The pulmonary artery and pulmonary capillary wedge pressures were monitored. The body temperature was recorded by a heat probe (Hewlett Packard, Viridia models Alto USA) placed in esophagus.

Anticoagulation with heparin 300 IU/kg (Nevparin® Mustafa Nevzat Istanbul Turkey) was provided 5 minutes prior to CPB. The adequacy of anticoagulation was monitored by activated clotting time (ACT) measurements performed in arterial blood samples with a Hemochron 1000. ACT level was kept above 450 sec. and additional heparin was given if needed. Following the termination of CPB, protamine sulphate (Protamin® Abbott Laboratories North Chicago USA) 3 IU/kg was administered to antagonise heparin until ACT value returned to normal.

The same brand of perfusion pumps (Stockert, SHRP 1010), membrane oxygenator and circulation lines were used in all cases. The priming solution contained NaCl 0.9% 20ml/kg, (Mediflex® Eczacıbaşı Baxter Istanbul Turkey), mannitol 20% 1,5cc/kg (Mannitol® Eczacıbaşı Baxter İstanbul Turkey), dexamethasone 8mg (Deksamet® Biosel İlaç Sanayi İstanbul Turkey) and NaHCO3 30mEq (Sodium Bicarbonate® Galen İlaç Sanayi İstanbul Turkey). The number of pumping cycles was adjusted to a flow rate of 2.4 L/min to attain a mean arterial pressure of 60 to 80 mmHg.

For myocardial protection, St. Thomas II cardioplegia solution (Plejisol® Abbott Laboratories North Chicago USA) containing 16 mEq/L of potassium was administered at a dose of 10-12 mL/kg from the aortic root with a pressure between 80 and 100 mmHg; the temperature of the solution was +4oC and the pH was neutralised by the addition of 20 mEq of bicarbonate per liter. Simultaneously topical cooling was applied by physiological saline at +4oC. Next, blood cardioplegia generated by the addition of 3.6 mEq potassium and 100 mL Plejisol into 300 mL of blood (containing 16 mEq/L potassium) was administered from the aortic root or the coronary sinus catheter. Immediately before the aortic cross-clamp was opened, terminal warm blood (5 mL/kg) at +36oC was given in an antegrade fashion.

Arterial blood samples were obtained from each participant every 30 minutes during the operation and after exiting from the perfusion pump. Blood gas analysis was performed with a Nova Stat 9 Profile analyser. Blood electrolytes, (Na,K,Cl,Ca), pH, PaO2, PaCO2, Hct, haemoglobin, blood glucose and lactate levels were measured and recorded.

At the start of the operation, while terminating the perfusion pump, and at postoperative 5 and 24 hours, arterial blood samples (5 cc) were obtained and centrifuged within 30 minutes after sampling (2500 rpm, 5 min International SBR USA). Next, the sera were kept at -80oC in deep freeze (Elektrolux MRF601/86 Frankfurt Germany).

S-100_ protein levels were analysed at the Department of Biochemistry, Marmara

University with S-100_ kits (Sangtec 100; AB Sangtec Medical Sweeden) and were measured with chemiluminescence technique by Diasorin Liason device

Patients transferred to cardiovascular intensive care unit postoperatively were extubated if their level of consciousness and respiratory parameters were appropriate.

Neurological examination and Mini Mental State Examination were performed preoperatively and 24 hours and 7 days postoperatively (3)

Questions directed to patients were accounted as either "true" or "false", and for each question 5 points were given out of a total score of 30. A score between 24 and 30 was considered normal cognition; 20 and 23, mild; 10 and 19 moderate; and 0 and 9 severe cognitive impairment. Stical Analyses was made by SPSS (Statistical Package for Social Sciences for Windows 10.0 was used for the statistical analyses of study data). Descriptive statistical methods (mean, standard deviation) were used, in addition to Student's test and Mann Whitney U test for the comparisons between quantitative data. Chi-square test and Fisher Exact chi-square test were used for the comparisons between qualitative data. The relationship between parameters was assessed by the Pearson correlation analysis. The results were presented with 95% confidence intervals, and p values less than 0.05 were considered significant.

RESULTS

The demographic characteristics of the patients are depicted in Table I.

Serum S-100_ levels at the beginning of the operation, before cardiopulmonary bypass (I), at the end of the cardiopulmonary bypass (II), and at the 5th (III) and 24th postoperative hours (III); patients' ages; cardiopulmonary bypass and cross-clamp times; and MMSE scores on the 1st and 7th postoperative days were compared.

Tablo I: Demographic characteristics of the patients and the significant factors of operations

Number of patients	33
Age (year)	32-73 (60,27±19,50)
Gender (F/M)	5/28
Mean arterial pressure (mmHg)	70,20±6,87
Operation time (minute)	216,45±43,60
CPB time (minute)	84,27±34,49
Cross- clamp time (minute)	53,32±24,22
Minimal temperature (oC)	28,04±1,15
Hypotermia time (minute)	52,32±28,12

Tablo II: The distribution of S100 _ at sampling time points

	Mean± SS
Pre CPB S100_ (mg/L)(I)	0,14±0,15
Post CPB S100_ (mg/L)(II)	2,61±2,90**
Postop 5th hours 100_ (mg/L)(III)	0,33±0,30
Postop 24th hours 100_ (mg/L)(IV)	0,26±0,22

****p<0,01 highly significant**

S-100_ levels measured before cardiopulmonary bypass (pre-CPB), after cardiopulmonary bypass (post-CPB), and at the 5th (Postop 5) and 24th (Postop 24) postoperative hours are shown in Table II. Post-CPB S-100_ levels (II) were significantly higher compared to Pre-CPB S-100_ (I) levels ($p < 0.01$).

The correlations between the S-100_ levels at the end of CPB (II) and the age, mean arterial blood pressure, operation time, CPB time, cross-clamp time, and minimal temperature and hypothermia times are shown (Table III).

A significant association between age and operation time and the increase in S-100_ levels post-CPB (II) was observed ($p < 0.01$). The duration of CPB had an important impact on the increase in S-100_ (II) ($p < 0.01$) (Table III).

MMSE and neurological examinations were performed preoperatively, and on postoperative days 1 and 7. No major neurological disorder

was detected in any patient. MMSE scores showed mild cognitive impairment in 9 patients on postoperative day 1 and in 3 patients on postoperative day 7 compared to preoperative levels. Moderate or severe cognitive impairment was not seen.

Tablo III: The distribution of S100 _ at sampling time points

	Post CPB S100	
	R	p
Age	0,518	0,014*
Mean arterial pressure	-0,314	0,154
Operation time	0,444	0,038*
CPB time	0,698	0,001**
Cross-clamp time	0,498	0,018*
Minimal temperature (oC)	-0,391	0,072
Hypothermia time	0,218	0,330

***p<0,05 significant; **p<0,01 highly significant**

The relationship between the change in MMSE on postoperative day 1 and the S100ß levels at the end of CPB (II) and at postoperative 5 (III) and 24 (IV) hours are shown in Table IV.

Tablo IV: Correlations with post-CPB S100_ levels

	MMSE Post-op day 1 Mild cognitive impairment		p
	+	-	
	20-23 (n=9)	points>23 points (n=24)	
S100ß (II) (_g/L)	4,61±3,66	1,21±0,79	0,004
S100ß(III) (_g/L) (post-operative 5th hours)	0,48±0,41	0,21±0,08	0,005*
S100ß (IV)(_g/L) (post-operative 24th hours)	0,38±0,29	0,17±0,11	0,013*

* p<0,05 significant; **p<0,01 highly significant

In 9 patients with mild cognitive impairment as demonstrated by MMSE scores, the S100b levels on the 5th and 24th postoperative hours were significantly higher compared to patients without cognitive impairment in the measurements simultaneously performed. (Table IV).

The relationship between the change in MMSE on postoperative day 7 and the S100b levels at the termination of CPB and at the 5th and 24th postoperative hours are demonstrated on Table (V).

Tablo V: The association between MMSE scores on the 7th postoperative day and S100, levels measured at the end of CPB, and at the 5th and 24th postoperative hours

	MMSE Post-op day 7 Mild cognitive impairment		p
	+	-	
	20-23 points (n=3)	>23 points (n=30)	
S100b (II) (_g/L)	5,16±5,08	1,85±1,09	0,025*
S100b(III) (_g/L) (post-operative 5th hours)	0,61±0,55	0,24±0,09	0,047*
S100b (IV)(_g/L) (post-operative 24th hours)	0,49±0,36	0,19±0,10	0,042*

*p<0,05 significant; **p<0,01 highly significant

Patients with mild cognitive impairment had significantly higher levels of S100b at the termination of CPB, and at the 5th and 24th postoperative hours compared to those without such impairment ($p < 0.05$).

In patients with mild cognitive impairment as measured by MMSE on postoperative day 1, the relationship between age, duration of operation ($p < 0.01$) and duration of CPB ($p < 0.05$) was statistically significant (Table VI).

Tablo V: The association between MMSE scores on the 7th postoperative day and S100, levels measured at the end of CPB, and at the 5th and 24th postoperative hours

	MMSE Post-op day 1 Mild cognitive impairment		p
	+	-	
	20-23points (n=9)	>23 points (n=24)	
Age (years)	65,44±9,76	57,69±15,32	0,004**
CPB time (min)	95,33±33,63	68,92±26,80	0,05*
Cross-clamp time (min)	56,11±18,05	45,23±19,75	0,204
Hypothermia time (min)	62,22±33,38	45,46±22,72	0,175
Operation time (min)	244,11±33,72	197,30±39,98	0,009**

*p<0,05 significant; **p<0,01 highly significant

In patients with mild cognitive impairment as measured by MMSE on postoperative day 7, age and the duration of operation were significantly different compared to those without cognitive impairment ($p < 0.05$). There were no significant differences with respect to cross-clamp time, hypothermia and operation time between those with and without mild cognitive impairment in MMSE on the 7th postoperative day ($p > 0.05$) (Table VII).

DISCUSSION AND CONCLUSION

In spite of the technical advances in anesthesia, cardiopulmonary bypass and surgical techniques, neurological complications are still the most important cause of morbidity in patients undergoing cardiac surgery. Neurological examination, computerised axial tomography and magnetic resonance imaging are the most widely used methods to diagnose cerebral injury. However these diagnostic methods are inapplicable during perioperative and early postoperative periods due to sedation, need for mechanical ventilation, failure to cooperate with the patient, and most importantly, hemodynamic fluctuations. Therefore, blood levels of certain proteins and substances released from neurons, glial cells and endothelium after cerebral ischemia and hypoxia have been used to detect cerebral injury (1).

S100ß released from astroglial cells has a distinct place among other markers owing to its specificity for cerebral tissue, early increase in plasma levels, blood-brain barrier permeability, and its ability to reflect brain injury .

The most important factor for the development of neurological and neuropsychological complications after cardiac surgery is the age of the patient. Although cerebral autoregulation is not lost in elderly patients, the stroke risk is higher, particularly in those with severe aortic stenosis or cerebrovascular diseases. Elderly people often have cognitive deficits; accordingly, slightest loss in cognitive functions may lead to an important disability in daily activities . In a series of 2417 cases reported by Wollman et al.(5) the average age of patients who developed neurological complications (n=273) after cardiac surgery was 70 ± 9 years.

Tuman et al. (6) retrospectively analysed 2000 patients undergoing coronary artery surgery and detected an overall postoperative neurological complication rate of 2.8%. In the same study, the percentage of patients with neurological complications was 8.9% in those over 75, 3.6% in patients between 65 and 74, and 0.9% in those younger than 65 y.

Jonsson et al. (7) studied 517 patients undergoing bypass operations and found that the levels of S100ß protein, which were higher in those with neurological injury, were significantly associated with advanced age. Kilminster et al.(8) examined 130 patients and reported that the increase in S100ß levels during and after CPB was higher in the elderly. Similarly, Westaby et al. (9) observed an increase in S100b protein levels that paralleled increasing age.

In our study, a significant relationship ($p < 0.05$) between S100b levels measured at the termination of CPB and advanced age (65 +) was detected in 33 cases (mean age: 60 ± 15.50, range: 32-73) who had no preoperative neurological disorders. In patients younger than 65 years of age, the preoperative serum S100b protein level of 0.11 ± 0.10 µg/L increased to 1.61 ± 1.20 µg/L after CPB. In patients ≥ 65 years of age the preoperative level was 0.13 ± 0.05 µg/L, and the postoperative level was 3.89 ± 3.8 µg/L. In patients older than 65 years of age who had higher S100b levels (n=9) minimal cognitive impairment was detected on postoperative day 1. Therefore, our findings suggest that

advanced age is an important predisposing factor for neurological complications occurring after cardiac surgery.

Another factor that plays a role in the neurological injury during or after cardiac surgery is the cross-clamp time and CPB time, which in turn cause an increase in the levels of S100b protein. Westaby et al.(9) compared two sets of patients; the first group of patients (n= 34) underwent coronary artery grafting under extracorporal circulation and the second group (n=9) underwent arterial grafting on the beating heart without extracorporal circulation. The extracorporeal circulation group had higher levels of S100ß (0.35±0.28µgr/L) compared to those without it (0.2±0.2µg/L), and the difference between the groups was significant ($p < 0.05$). Again, in the same study a significant association between the duration of perfusion and the S100_ levels at the end of perfusion was noted in the extracorporal circulation group ($p < 0.05$).

Jonsson et al.(7) have examined 517 cases undergoing cardiac surgery and found that the CPB time in those with postoperative stroke (96.5 ± 50 min) was more prolonged than in those without stroke (75 ± 24 min) ($p < 0.05$), and that the S100_ protein levels correlated with the prolongation in the CPB time ($p < 0.05$). Also in another study with 130 patients, the release of S100_ protein during and after cardiopulmonary bypass was positively correlated with the perfusion time (8). All studies examining the cerebral complications of cardiopulmonary bypass indicate that advanced age and the prolonged CPB time are associated with neurological and neurocognitive impairments.(1,2,,6,7,8,10,11).

In our study, the mean concentration of S100_ protein in the overall patient group undergoing cardiopulmonary bypass was 0.14±0.15_g/L preoperatively, and this value increased to 2.61±2.90_g/L at the end of the cardiopulmonary bypass ($p < 0.01$). Although a decrease at the 5th postoperative hour was noted (0,33±0,30_g/L), this value was still higher compared to preoperative levels ($p < 0.05$).

The rapid increase at the end of bypass results from cerebral and extra cerebral factors. The rapid fall is due to rapid elimination of S100_ protein, and the temporary increase in the levels of S100_ protein without clinical neurological signs and symptoms is due to the increase in the permeability of the blood-brain barrier resulting from microemboli or complement activation, rather than to cerebral injury (2).

Elevated S100_ protein levels postoperatively were shown to be associated with intraoperative cerebral microemboli in a transcranial Doppler study(12). Oxford group, in their comparative study, has reported that the use of arterial filters was able to prevent the abnormal peak levels of S100_ protein observed at the end of cardiac surgery(13). In another study by the same investigators, it has been shown that intracardiac surgery (mitral or aortic valve surgery) was associated with higher postoperative plasma levels of S100_ protein compared to coronary artery surgery(14).

In our study, arterial filters were used in all cases with the aim of preventing microemboli.

The heat regimen used during cardiac surgery, the minimum body temperature, the duration of hypothermia, and the speed of warming were also investigated in terms of their possible effect on the neurological outcome.

In this study, all patients were operated under moderate hypothermic conditions (28-32 oC) and the minimal body temperature was 28,4± 1,15oC. Consequently, no increase in S100_ levels due to deep hypothermia or cases of neurological injury have been observed.

Neurological examination performed preoperatively and on postoperative days 1 and 7 revealed no pathological findings. The Mini Mental State Examination (MMSE) showed mild cognitive impairment in 9 patients on postoperative day 1 (MMSE score 20-23). Of these 9 cases, 5 still had neurocognitive impairment on the 7th postoperative day.

Kilminster et al.(8) studied a group of cardiac surgery patients (n=130) between 60-70 years of age most of whom underwent coronary artery bypass grafting, and found that the elevated S100_ protein concentrations were associated with advanced age, bypass time and the impairment in the neurocognitive tests (Rey auditory-verbal learning test) performed 60 days after the operation.

Basile et al.(15) in a smaller study (n=16) found an association between age and cognitive changes. In their study, Mini Mental State Examination and Randt Memory Test were used. Patients were classified into two groups on the basis of their age (< 69 y and ≥ 69 y) and cognitive impairment correlated with advanced age.

Herman et al.(16) in a study with 74 patients have shown that S100_ and neuron specific enolase were directly related to neuropsychological and neuropsychiatric outcome following cardiac surgery.

In the present study, S100_ protein level was in the normal range in all patients at the beginning of the surgery (0.14 ± 0.15 µg/L), and it showed a significant increase to 2.61 ± 2.90 µg/L after CPB ($p < 0.001$). Nineteen of 33 patients had higher levels than normal (<0.50 µg/L). The concentrations of S100_ at the 5th postoperative hour (0.33 ± 0.30 µg/L) were higher compared to preoperative levels, though they were in the normal range ($p < 0.05$), except for 5 patients. The S100_ protein levels at the 24th postoperative hour were higher compared to preoperative levels, and in only 3 patients the levels were above the normal range. However, this increase was not statistically significant (0.26±0.22_g/L)($p>0.05$).

In 9 cases mild cognitive impairment as measured by MMSE was detected on the 1st postoperative day, which persisted in 5 patients on the 7th postoperative day. The serum levels S100_ in patients with mild cognitive impairment on the 1st postoperative day were higher than those without it at the end of CPB (4.61±3.36 _g/L;1.21±0.79 _g) ($p<0.01$), at the 5th postoperative hour (0.48±0.41_g/L; 0.21±0.08 _g/L) ($p<0.01$), and at the 24th postoperative hour (0.38±0.29_g/L; 0.17±0.11 _g/L) ($p<0.05$). There was a significant association between the cognitive impairment on the 1st postoperative day and age, CPB time and the operation time; and there was a significant association between the cognitive impairment on the 7th postoperative day and age and CPB time.

Of the 5 patients with cognitive impairment persisting on the 7th postoperative day, 2 had S100_ levels higher than normal (0.66_g/L, 0.59_g/L). Of these 5 patients 4 were older than 69 years of age and had prolonged CPB and cross-clamp times. the fifth case was 56 years of age but had prolonged CBP and cross-clamp times too.

Neurological complications arising from cardiac surgery cause a significant increase in morbidity, mortality and resource utilization. As has been emphasized in many published studies, while the incidence of perioperative stroke is around 1-5%, the incidence of neurocognitive changes can reach up to 80%, resulting in permanent cognitive dysfunction in almost one third of the elderly cases (1,2). The recent advances in the field of cardiac anesthesia and surgery allow more complicated or older patients with cardiac and concomitant pathologies to be operated. Neurological injury

during cardiac surgery can result from many factors including advanced age, concomitant cerebrovascular disorders, diabetes mellitus, renal pathologies, aortic atheromatous diseases, cardiopulmonary bypass time, perfusion pressure, flow and pulsation, temperature and acid/base management.

In our study, an important biochemical marker, S100_ protein levels were used to evaluate the perioperative and early postoperative neurological injury in patients operated with CPB technique. In patients with minimal cognitive impairment a significant relationship between S100_ protein levels and age, cross-clamp time and CPB time was observed.

We conclude that in high-risk patients undergoing CPB, S100_ levels are useful in the evaluation of perioperative and early postoperative neurological injury and can be used to estimate the degree of cerebral injury and to provide cerebral protection.

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